BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

A&A Ref: 57661

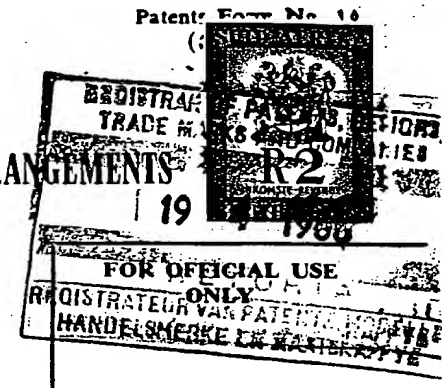
6617

ADAMS & ADAMS,
Allied Building,
Pretoria.

REPUBLIC OF SOUTH AFRICA

Patents Form No. 16

THE PATENTS ACT, 1952, AS AMENDED.



APPLICATION FOR A PATENT UNDER INTERNATIONAL ARRANGEMENTS

(WITH AUTHORISATION OF AGENT)

change I.t.O. request 7-10-70.

Filing date and Application No. 68/2530

Full Name(s) of applicant(s): SCHERING AKTIENGESELLSCHAFT, a Body Corporate organized and existing under the laws of the Federal Republic of Germany, of Berlin and Bergkamen, Germany and Waldstrasse 14, D4619 Bergkamen Germany.

Address(es) of applicant(s): ~~address for service~~ Müllerstraße 17o/172
D 1 Berlin 65, Germany,

Full Name(s) of inventor(s): Joachim Ufer, Karl-Heinz Kimbel and Ursula Lachnit

I/We do hereby declare that I am/we are in possession of an invention the title of which is

"Method for contraception"

I am/We are the assignee(s)/~~legal representative(s)~~ of the inventor(s). Application(s) for protection for the invention has/have been made in the following country/countries and on the following official dates i.e.:-

1.	(country)	Germany	(date) 19th April, 1967	(number)	Sch 40 583 IVa/30h
2.	(country)		(date)	(number)	
3.	(country)		(date)	(number)	

The said application or each of the said applications was the first application in a convention country in respect of the relevant invention by me/us or by any person from whom I/we derive title. To the best of my/our knowledge and belief there is no lawful ground for objection to the grant of a patent to me/us on this application. I/We pray that a patent be granted to me/us for the investion in priority over other applicants and that such patent shall have the official date of the first application in a convention country i.e. 19th April, 1967.

I/We hereby appoint the partners and qualified staff of the firm of ADAMS & ADAMS, jointly and severally, to act for me/us in all matters relating to this application and any letters patent granted thereon.

Dated this 1st day of April 1968

FIRST RECEIVED BY ME IN THE REPUBLIC OF SOUTH AFRICA THIS 8th DAY OF April 1968

Address for service:
C/o ADAMS & ADAMS,
ALLIED BUILDING,
PRETORIA.

FOR REVENUE ONLY
SOUTH AFRICA 10c SUID-AFRIKA

M. Ufer

SCHERING AKTIENGESELLSCHAFT

Signature of Applicant/s and Capacity

(Dr. Asmis) (Dr. Mattner)
(CONFIDENTIAL CLERKS)

Table of Classification	
Class	Sub-Class

PATENTS
FORM NO. 3

A. & A. Ref. No. 57661

ADAMS & ADAMS
PATENT ATTORNEYS
ALLIED BUILDING
PRETORIA

REPUBLIC OF SOUTH AFRICA

The Patents Act, 1952

COMPLETE SPECIFICATION

68/2530

Here insert (in full) name, address of applicant(s) as in application form. (a)

SCHERING AKTIENGESELLSCHAFT, a Body Corporate organized and existing under the laws of the Federal Republic of Germany, of Berlin and Bergkamen, Germany,
Müllerstrasse 170/172, D 1 Berlin 65, Germany.
and Waldshaese 14, D4619 Bergkamen Germany

Here insert title (verbally agreeing with that in the application form.) (b)

"METHOD FOR CONTRACEPTION"

I/WE do hereby declare this invention, the mann r in which and the method by which it is to be performed, to be particularly described and ascertained in and by the following statement:-

Hormonal methods for contraception are already known, for example the oral application of Enovid (R), Ovulen (R), Anovlar (R) and similar combinations of oestrogenically and gestagenically active principles. Also known are tests with corresponding injection preparations, with which the active principle components have an additional accumulative effect. The action of these known agents is based on the fact that the active principle used inhibits the ovulation. The contraception obtained with these known methods is based therefore on the inactivation of the ovaries and the discontinuation of the bleeding caused by these methods does not correspond to a normal menstruation. Apart from the known undesired side effects, such as for example stomach troubles, vomiting, increase of weight and others, the application of the known methods means a far-reaching interference with the endocrinological conditions of women, as every expert will know.

It has now been found that a reliable contraception can be achieved without a simultaneous suppression of the ovulation, after a single application of a gestagen, when the application of the active principle is made parenterally, with which the duration of activity, namely for a menstruation cycle or a longer period, can be varied by the utilisation of an active principle with an accumulative effect or by variation of the quantity of the dose of the gestagen administered.

The invention relates therefore to a method for contraception without the suppression of ovulation, characterised in that a suitable gestagen is applied parenterally, preferably intramuscularly or subcutaneously or by implantation.

As active principles suitable for the method according to the invention, use can be made of all gestagens which, after parenteral application or implantation, do not cause inhibition of ovulation. With the practical application of the method

according to the invention, the dosing of the active principle is chosen in such a way that the gonadotropin secretion is not or only slightly suppressed.

Particularly suitable are such active principles which, apart from their gestagenic action, have no central inhibiting effect, more particularly an ovulation inhibiting effect, for example esters of hydroxy-progesterone and of 19-nor-hydroxy-progesterone and more particularly the corresponding 17-capronates or 17-oenanthates.

Suitable are also such active principles the desired gestagenic effect (and the anti-oestrogenic effect) of which is considerably dissociated from the undesired ovulation inhibiting effect. For application according to the invention, these active principles are dosed in such small quantities that, on the one hand, the change of the composition and texture of the cervical mucus obtained in this manner is sufficient to effect a reliable contraception and, on the other hand, the threshold dosage of the central inhibiting effect is not exceeded. The following gestagens are mentioned as examples: progesterone and its pharmaceutically effective 3-enol ester or 17 alpha-hydroxy-progesterone derivatives, such as for example the 17-esters of 6alpha-methyl-17alpha-hydroxy-progesterone, 6-methyl-6-dehydro-17alpha-hydroxy-progesterone, 6-chloro-or fluoro-6-dehydro-17alpha-hydroxy-progesterone, 6-chloro- or fluoro-6-dehydro-16alpha- or 16beta-methyl-17alpha-hydroxy-progesterone, 6,16-dimethyl-6-dehydro-17alpha-hydroxy-progesterone, 6-methyl- or 6-chloro-6-dehydro-16-methylene-17alpha-hydroxy-progesterone, 1,2-methylene-6-chloro- or 6-fluoro-6-dehydro-17alpha-hydroxy-progesterone or also 17alpha-ethinyl-18-homo-19-nor-testosterone and their esters.

Applicable in principle are also gestagens of which the

dissociation between the desired gestagenic effect and the undesired ovulation inhibiting effect is relatively close, such as for example nor-ethisterone capronate, 17alpha-ethinyl-testosterone, 17alpha-ethinyl-19-nor-testosterone, 17alpha-ethinyl-delta$^{5(10)}$-oestren-17beta-ol-3-one, 17alpha-methyl-19-nor-testosterone, 17alpha-ethinyl-delta^{4}-oestren-3, 17beta-diol, 17alpha-ethinyl-delta^{4}-oestren-17beta-ol, 17alpha-alkyl-delta^{4}-oestren-17beta-ol and their physiologically effective esters. For the practical application of the method according to the invention, these last-named active principles are however less suitable, because as a result of the considerably smaller dissociation of the gestagenic effect from the ovulation inhibiting effect, they are difficult to dose.

If the gestagens applicable according to the invention are used in the form of their esters, use can be made of all physiologically valuable straight-chain or branched-chain esters, such as for example the acetates, valerianates, butyrates, capronates, oenanthates, undecylates, and the like. Furthermore, the ester residue present can also be substituted in known manner, for example by one or more halogen atoms, hydroxyl, carbonyl, keto, amino, and similar groups.

With the application of the method according to the invention in which the active principle is applied about 5 to 7 days after the start of the bleeding, the duration of the activity is at least for the period of a menstruation cycle. With a corresponding dosage of the active principle, or by utilising a gestagen with accumulative effect, also a correspondingly longer duration of activity can be obtained, for example, for 3 to 4 months and more.

More particularly for the active principles of the first

group, without central inhibiting effect, and essentially also for the active principles of the second group (considerable dissociation of the gestangenic from the ovulation inhibiting effect) the active dose is generally between 3-250 mg of gestagen. In many cases, more particularly when the duration of the effect is to be limited to only one menstruation cycle, a dosage of up to about 100 mg is already sufficient. For ensuring contraception for a longer duration by a single application of gestagen, more particularly the gestagens of the first group can be administered in dosages of up to 500 mg.

With the utilisation of 19-nor-17alpha-hydroxy-progesterone capronate, the dose is from 3 to 20 mg, preferably about 5 mg and with the utilisation of 17alpha-hydroxy-progesterone capronate 75 to 150 mg, preferably about 100 mg, when the duration of activity of the method according to the invention is to cover one menstruation cycle.

An advantage of the method according to the invention is that the contraception is brought about without a simultaneous ovulation inhibition and, apart from the modification of the composition and structure of the cervical mucus, all biological and physiological phenomena of the sexual cycle remain uninfluenced. Side effects (which may occur as is known with the application of methods, for example a combination of active principles to be applied orally, in which the resulting contraception is based on the ovulation inhibiting effect of the active principle), for example stomach troubles, vomiting, increase of weight etc., are not observed with the application of the method according to the invention.

For the practical application of the method according to the invention, the active principle is preferably dissolved in a solvent suitable for parenteral injection as known to a skilled

person for such purposes, filtered sterile and filled into ampulla under aseptic conditions. Particularly suitable are oily solvents, such as for example sesame oil or castor oil. Apart from these solvents vegetable oils are also suitable, such as linseed oil, cotton seed oil, sunflower oil, arachid oil, olive oil, wheat oil, etc. For increasing the solubility of the active principles, diluting agents or dissolution promoters, such as for example benzyl benzoate, may be added to the oily solutions.

Apart from the said oily solvents, use can however also be made of synthetic solvents such as, for example, glycol, lactic acid ester, benzul alcohol etc. The possible solvents mentioned above, of course are not exhaustive. This does not seem to be necessary because the expert is in a position, by reason of his professional knowledge, to choose from among the known solvents the most suitable for the purpose.

EXAMPLE 1.

5 g of 19-nor-17alpha-hydroxy-progesterone capronate are dissolved in sesame oil. The solution is made up with sesame oil to 1000 ml, filtered sterile and filled into 1 ml ampullae under aseptic conditions. Thereafter it is after-sterilised for 2 hours at 120°C.

EXAMPLE 2.

20 g of 19-nor-17alpha-hydroxy-progesterone capronate are dissolved in a mixture of castor oil/benzyl benzoate (6 : 4) and the solution is then made up to 1000 ml. The sterile filtered solution is filled in known manner into 1 ml ampullae under aseptic conditions. The ampullae are finally after-sterilised for 2 hours at 120°C.

EXAMPLE 3.

150 g of 17alpha-hydroxy-progesterone capronate are dissolved in a mixture of castor oil/benzyl benzoate (6 : 4) and then made up to 1000 ml of solution. The sterile filtered solution is, in known manner, filled into 1 or 2 ml ampullae under aseptic conditions. The ampullae are then after-sterilised for 2 hours at 120°C.

Having now particularly described and ascertained our said invention and the manner in which the same is to be performed, we declare that what we claim is:

1. A method for achieving contraception without the suppression of ovulation, characterised in that a suitable gestagen is administered parenterally, preferably intra-muscularly or subcutaneously.

2. A method in accordance with claim 1, characterised in that the active principle is administered in oily solution, preferably in sesame oil or castor oil, if desired in the presence of a dissolution promoter or dilution agent, for example benzyl benzoat

3. A method in accordance with claim 1, characterised in that the active principle is administered by implantation.

4. A method in accordance with any one of claims 1 to 3, characterised in that gestagens, which have no additional ovulation inhibiting or central inhibiting effects are used as the active principle.

5. A method in accordance with any one of claims 1 to 4, characterised in that as active principle hydroxy-progesterone or 19-nor-hydroxy-progesterone ester is used.

6. A method in accordance with any one of claims 1 to 5, characterised in that as active principle hydroxy-progesterone or 19-nor-hydroxy-progesterone capronate is dispensed.

7. A method in accordance with any one of claims 1 to 3, characterised in that as active principle, a gestagen is used with sufficient dissociation of the desired gestagenic effect from the undesired central inhibiting effect or ovulation inhibiting effect, at a dosage which with complete contraceptive effect does not reach the threshold dosage of the side effect.

8. A medicament for contraception, containing a gestagen in a dosage which does not suppress or which only slightly suppresses the gonatropin secretion.

9. A medicament in accordance with claim 8, containing an active principle in accordance with claim 5 or 6.

10. A medicament in accordance with claim 8 or 9, containing as active principle 19-nor-17alpha-hydroxy-progesterone capronate at a dosage of 3 to 25 mg, preferably about 5 mg.

11. A medicament in accordance with claim 8 or 9, containing as active principle 17alpha-hydroxy-progesterone capronate at a dosage of 75 to 150 mg, preferably about 100 mg.

12. A method for achieving contraception, substantially as described herein.

13. A medicament for contraception, substantially as described herein.

DATED THIS 19th DAY OF APRIL 1968

PATENT ATTORNEY